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ORIGINAL ARTICLE

Prediabetes defined by HbA_{1c} and by fasting glucose: differences in risk factors and prevalence

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Abstract

Aims To investigate, in a sample of nondiabetic adults from a Spanish community, the differences between prediabetes as defined by HbA_{1c} ("H-prediabetes") and by fasting plasma glucose (FPG) ("F-prediabetes") in regard to prevalence and the influence of potential risk factors, adjusting the latter for confounders.

Methods A total of 1328 nondiabetic participants aged ≥ 18 years were classified as normoglycemic, H-prediabetic [HbA_{1c} 5.7–6.4% (39–47 mmol/mol)] or F-prediabetic (FPG 5.6–6.9 mmol/L). Multivariable analyses were used to compare the impacts of risk factors on the prevalence of H-prediabetes, F-prediabetes and their conjunctive and disjunctive combinations ("HaF-prediabetes" and "HoF-prediabetes," respectively).

Results Some 29.9% of participants were HoF-prediabetic, 21.7% H-prediabetic, 16.3% F-prediabetic and only 8.1% HaF-prediabetic. Whatever the definition of prediabetes, increasing age, fasting insulin and LDL cholesterol were each a risk factor after adjustment for all other variables. Increasing BMI and decreasing mean corpuscular hemoglobin (MCH) were additional risk factors for H-prediabetes; male sex and increasing uric acid for F-prediabetes and increasing BMI for HaF-prediabetes. The participants satisfying the compound condition "hypertension or hyperlipidemia or obesity or hyperuricemia" (59.9% of the whole study group) included 83.1% of all subjects with HoF-prediabetes.

Conclusions In this population, the most sensitive risk factor for detection of prediabetes was age, followed by fasting insulin, LDL cholesterol, BMI, MCH, male sex and uric acid, with differences depending on the definition of prediabetes. MCH, an indirect measure of erythrocyte survival, significantly influences the prevalence of HbA_{1c}-defined prediabetes. This study suggests that screening of individuals with selected risk factors may identify a high proportion of prediabetic persons.

Keywords Community screening · FPG · HbA_{1c} · Prediabetic phenotype · Risk factors · Prevention

Abbreviations

ADA	American Diabetes Association
AEGIS	The A Estrada Glycation and Inflammation Study
CI	Confidence interval
FPG	Fasting plasma glucose

Managed by Massimo Porta.

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F-prediabetes	Prediabetes according to the FPG criterion (FPG 5.6–6.9 mmol/L)
GMA drugs	Pharmaceutical drugs affecting glucose metabolism
HbA_{1c}	Glycated hemoglobin
H-prediabetes	Prediabetes according to the HbA_{1c} criterion [HbA_{1c} 39–46 mmol/mol (5.7–6.4%)]
HaF-prediabetes	Prediabetes according to both the FPG and HbA_{1c} criteria
HoF-prediabetes	Prediabetes according either the HbA_{1c} or the FPG criterion, or both
IFG	Impaired fasting glucose
OGTT	Oral glucose tolerance test

Introduction

The term "prediabetes" is defined by the American Diabetes Association (ADA) as a state of high but subdiabetic glycemia as indicated by a fasting plasma glucose (FPG) value of 5.6–6.9 mmol/L (impaired fasting glucose, IFG), a plasma glucose value of 7.8–11.0 mmol/L in a 2-h oral glucose tolerance test (OGTT) or an HbA_{1c} value of 5.7–6.4% (39–46 mmol/mol) [1]. The identification of individuals with prediabetes provides an opportunity for intervention through lifestyle modification and pharmacological interventions to prevent progression to diabetes [2, 3]. The lower limits of the above ranges attempt to achieve a definition of prediabetes that strikes an adequate balance between sensitivity (to include persons who would benefit from prevention strategies) and specificity (to avoid the inclusion of persons at relatively low risk, for whom intervention may not be cost-effective). Owing to its complexity and poor reproducibility, the OGTT has in many centers been abandoned except for screening for gestational diabetes [4]. Accordingly, in this paper, we concentrate on the HbA_{1c} and FPG criteria of prediabetes. As is well known, these criteria are discordant in that, for a given population, they diagnose prediabetes in groups that are different, though overlapping [5]. This is due to FPG and HbA_{1c} being influenced to different extents by numerous factors, including age, sex, red blood cell lifetime, ethnicity, pharmaceutical drugs, the duration of fasting and factors that interfere with their measurement [2, 6, 7].

A great number of studies have investigated the prevalence of prediabetes according to different definitions in a variety of ethnic groups, while others have proposed HbA_{1c} cutoffs for a variety of different glucose intolerance groups [8–15]. Others again have compared the different definitions of prediabetes in regard to their ability to predict either progression to diabetes or the development of other major illnesses favored by diabetes, such as kidney disease and cardiovascular disease [7, 16–20]. However, as far as we know, none of these objectives has been pursued while adjusting for a broad range of risk factors for diabetes.

Here, we report the results of a community-based study of ethnically homogeneous nondiabetic adults in which we (1) evaluated the prevalence of prediabetes according to the relevant ADA cutoffs for HbA_{1c}, FPG and their disjunctive and conjunctive combinations; (2) determined independent risk factors for prediabetes under the alternative definitions of the latter by means of multiple logistic regression models with full adjustment and (3) examined the proportion of prediabetic subjects contained in various groups defined by risk factors for diabetes.

Methods

Subjects

The subjects taking part in this study were a subset of the participants in the A Estrada Glycation and Inflammation Study (AEGIS; trial NCT01796184 at www.clinicaltrials.gov), an epidemiological study of the relationships between, on the one hand, various tests of dysglycemia and inflammation, and on the other, the risk of progression to diabetes and cardiovascular disease [21]. On paper, the initial candidates for entry in AEGIS were an age-stratified random sample of 3500 men and women aged 18 years or more that was drawn from among residents in the northwest Spanish municipality of A Estrada who were registered in Spain's virtually 100% comprehensive national health system. Of these, 2230 were accessible, 1516 of whom agreed to participate in AEGIS. Those included in the present substudy were the 1328 (87.7%) who had FPG < 7 mmol/L and HbA_{1c} < 6.5% (48 mmol/mol) at screening for entry and had never been told by a doctor or other health professional that they had diabetes, other than during pregnancy (Fig. 1).

Laboratory assays

Glucose was determined in plasma samples from fasting participants by the glucose oxidase peroxidase method. Triglycerides, HDL, LDL, total cholesterol, creatinine and uric acid were determined on a fully automatic analyzer (ADVIA 2400 from Siemens Healthcare Diagnostics, Barcelona, Spain). Fasting insulin was determined by an immunochemometric assay on a Siemens ADVIA Centaur (Siemens Healthcare Diagnostics, Barcelona, Spain). Mean corpuscular hemoglobin (MCH) was determined on an ADVIA 2120 automated hematology analyzer (Siemens Healthcare Diagnostics, Barcelona, Spain). HbA_{1C} was determined by high-performance liquid chromatography on a Menarini Diagnostics HA-8160 analyzer; all HbA_{1C} values were converted to DCCT-aligned values [22].

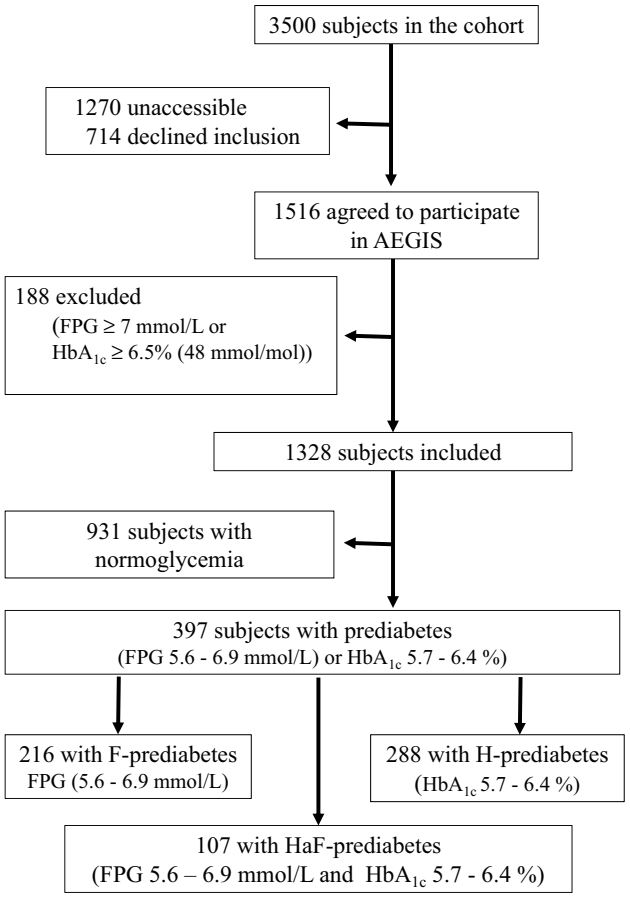

Fig. 1 Patient selection flow diagram

All laboratory analyses were performed on the day of sample collection in the Clinical Biochemistry Laboratory of the University Hospital Complex, Santiago de Compostela, Spain. BMI and blood pressure were measured following standard protocols. Age, sex, smoking status and use of medication were reported at study visits. Hypertension was identified by the use of blood pressure-lowering medication, by systolic blood pressure ≥ 140 mm Hg (mean of two measurements taken at a study visit), or by diastolic blood pressure ≥ 90 mm Hg (*idem*).

Group definitions and statistical analyses

Following ADA, participants with FPG < 5.6 mmol/L and HbA1C < 5.7% (39 mmol/mol) were considered normoglycemic. Among the other (prediabetic) participants, the following overlapping groups were defined: H-prediabetic participants [HbA_{1c} 5.7–6.4% (39–46 mmol/mol)], F-prediabetic participants (FPG 5.6–6.9 mmol/L), HaF-prediabetic participants [HbA_{1c} 5.7–6.4% (39–46 mmol/mol) and FPG 5.6–6.9 mmol/L] and HoF-prediabetic participants [HbA_{1c} 5.7–6.4% (39–46 mmol/mol) or FPG 5.6–6.9 mmol/L, or both]. "Prediabetic" without a prefix is used for HoF-prediabetes when there is no danger of confusion and for the general concept of prediabetes.

All variables were checked for normality. Data for normally distributed continuous variables are summarized as means ± SDs and those for other continuous variables as medians with interquartile ranges in parentheses. The statistical significance of differences between groups was estimated by Student's *t* test for normally distributed variables and nonparametrically otherwise. Multivariable logistic regression analyses were used to evaluate association between each prediabetes group (HoF-, H-, F- and HaF-prediabetics) and various possible risk factors (age, sex, current smoking status, systolic and diastolic blood pressures, BMI, HDL and LDL cholesterol, triglycerides, MCH, fasting insulin, creatinine, uric acid and use of pharmaceutical drugs affecting glucose metabolism). The odds ratios presented for each variable are adjusted for all the other variables. General linear models were fitted to the FPG-age and HbA_{1c}-age data, and their predictions for mean FPG and mean HbA_{1c} in various age groups were compared with those of models adjusting for sex, BMI, fasting insulin, LDL cholesterol, uric acid, MCH and, in the case of HbA_{1c}, FPG; for HbA_{1c}, a model adjusting only for FPG was also run. Pairwise correlations between variables were calculated as Pearson's *r*. All statistical analyses were performed using SPSS 22 (SPSS, Chicago, IL). *P* values ≤ 0.05 were considered statistically significant.

Results

Table 1 summarizes demographic, clinical and biochemical characteristics of the normoglycemic participants (70.1%) and the various groups of prediabetic participants. 21.7% of all participants were H-prediabetic, 16.3% F-prediabetic and only 8.1% HaF-prediabetic. There were statistically significant differences between normoglycemic and prediabetic participants in regard to all the variables of Table 1 except the proportion of women and MCH. 48.6% of participants were taking drugs that affect glucose metabolism (hereinafter "GMA drugs": statins, beta blockers, diuretics, calcium channel blockers, ACE inhibitors, angiotensin II receptor blockers, antidepressants, glucocorticoids or thyroid drugs), and in this subgroup, H-prediabetes was significantly more prevalent than F-prediabetes (30.1% vs 19.5%, $P < 0.001$), whereas in the subgroup that were not taking these drugs, the prevalences of H- and F-prediabetes were very similar (13.8% and 13.2%, respectively, $P = 0.63$). As might be expected, those who took these drugs were on average older than those who did not (57 ± 18 years vs 44 ± 15 years, $P < 0.001$).

Table 1 Characteristics of the normoglycemic group and the various prediabetic groups

Variables	Normoglycemic	Prediabetic[a]			
		HoF-prediabetic	H-prediabetic	F-prediabetic	HaF-prediabetic
n (%)	931 (70.1)	397 (29.9)	288 (21.7)	216 (16.3)	107 (8.1)
Age, years	44 (33–58)	63 (52–72)*	64 (53–72)*	63 (52–71)*	65 (57–71)*
Women	540 (58)	217 (54.7)	176 (61.1)	101 (46.8)†	60 (56.1)
Use of GMA drugs[b]	397 (42.6)	248 (62.5)*	194 (67.4)*	126 (58.3)†	72 (67.3)*
Current smoker	242 (26)	48 (12.1)*	35 (12.2)*	23 (10.6)*	10 (9.3)†
BMI, kg/m^2	26.6 ± 4.6	30.5 ± 4.7*	30.6 ± 4.7*	30.7 ± 4.3*	31.3 ± 3.9*
Obese, ≥ 30 kg/m^2	206 (22.1)	210 (52.9)*	152 (52.8)*	127 (58.8)*	69 (64.5)*
MCH (pg)	29.7 ± 1.8	29.7 ± 1.7	29.4 ± 1.7†	30.0 ± 1.6†	29.7 ± 1.6
Creatinine (μmol/L)	63.5 ± 15.2	65.5 ± 14.8‡	65.1 ± 15.3	66.5 ± 13.6‡	66.3 ± 14.0
Uric acid (mmol/L)	297 ± 88	341 ± 86*	336 ± 86*	355 ± 88*	357 ± 90*
Hyperuricemia, ≥ 6 mmol/L	224 (24.1)	163 (41.1)*	112 (38.9)†	103 (47.7)*	52 (48.6)*
Systolic blood pressure (mmHg)	125 ± 15	137 ± 16*	137 ± 16*	137 ± 15*	140 ± 14*
Diastolic blood pressure (mmHg)	76 ± 9	80 ± 9*	80 ± 9*	81 ± 8*	81 ± 9*
Total cholesterol (mmol/L)	50.7 ± 9.8	53.5 ± 9.8*	53.4 ± 9.2*	54.0 ± 10.0*	54.2 ± 8.8†
HDL cholesterol (mmol/L)	15.9 ± 4.5	15.3 ± 4.3‡	15.4 ± 4.4	15.0 ± 3.8‡	15.0 ± 3.8
LDL cholesterol (mmol/L)	29.5 ± 7.9	32.0 ± 8.2*	31.9 ± 7.6*	32.8 ± 8.7*	33.2 ± 7.9*
Triglycerides (mmol/L)	0.99 (0.73–1.33)	1.22 (0.88–1.70)*	1.22 (0.89–1.66)*	1.26 (0.90–1.80)*	1.27 (0.98–1.72)*
Fasting insulin (mU/L)	9.6 (6.7–12.8)	13.4 (9.3–18.1)*	12.8 (9.1–17.1)*	14.7 (10.5–20.7)*	15.4 (11.5–20.8)*
FPG (mmol/L)	4.7 ± 0.4	5.5 ± 0.6*	5.4 ± 0.6*	5.9 ± 0.4*	6.1 ± 0.4*
HbA_{1c} (%)	5.3 ± 0.2	5.7 ± 0.3*	5.9 ± 0.2*	5.7 ± 0.3*	5.9 ± 0.2*
HbA_{1c} (mmol/mol)	34 ± 3	39 ± 3*	40 ± 2*	38 ± 4*	41 ± 2*

Data are *n*, *n* (%), mean ± SD or median (interquartile range)

[a]H, HbA_{1c} 5.7–6.4% (39–47 mmol/mol); F, FPG 5.6–6.9 mmol/L; HaF, HbA_{1c} 5.7–6.4% (39–47 mmol/mol) and FPG 5.6–6.9 mmol/L; HoF, HbA_{1c} 5.7–6.4% (39–47 mmol/mol) or FPG 5.6–6.9 mmol/L

[b]Pharmaceutical drugs that can affect glucose metabolism

*$P < 0.001$; $^{\dagger}P < 0.01$; $^{\ddagger}P < 0.05$ for comparison with subjects with normoglycemia

Female sex, current smoking and the use of GMA drugs were each more prevalent among H-prediabetics than among F-prediabetics, while the reverse was held for obesity and hyperuricemia. 23.2% of women were H-prediabetic as against 13.3% who were F-prediabetic ($P < 0.001$), but there was no such difference for men (19.6% H, 20.1% F, $P = 0.83$). HaF-prediabetic participants were more likely to be obese and had higher insulin levels than those who were H- or F-prediabetic but not both ($P < 0.01$ for both variables). More prediabetic participants were H-prediabetic than F-prediabetic (72.5% as against 54.4%, $P < 0.001$) and the same held for most of the subgroups studied (Supplementary Table 1). The exceptional subgroups in this respect were men, participants younger than 45 years, hyperuricemic participants, those taking no GMA drugs, those taking diuretics and those taking ACE inhibitors.

Strikingly, although in all BMI strata, more HoF-prediabetics were H-prediabetics than were F-prediabetics, the proportion who were H-prediabetic decreased with increasing BMI, whereas the proportion who were F-prediabetics increased (Supplementary Table 1). This trend in the relative prevalence of F-diabetes paralleled the trend of fasting insulin, which rose from 8.3 ± 3.6 mU/L among participants with BMI < 25 kg/m^2 to 16.2 ± 8.9 mU/L among those with BMI ≥ 30 kg/m^2; and although FPG correlated with BMI slightly better than did HbA_{1c} ($r = 0.39$ as against 0.36), the reverse held after adjustment for fasting insulin ($r = 0.31$ for HbA_{1c} vs BMI, $r = 0.26$ for FPG vs BMI). In fact, FPG correlated better with fasting insulin than it did with HbA_{1c} ($r = 0.37$ as against 0.19, $P < 0.001$).

The prevalence of H-prediabetes did not vary significantly between men and women and nor did that of HaF-prediabetes, but men were much more likely than women to have F-prediabetes ($P < 0.001$), especially in the age decades between 30 and 60 years (Supplementary Table 2). In all six age groups, H-prediabetes was more prevalent than F-prediabetes; and the increase in prevalence with the age of the age group, though evidenced by both HbA_{1c} and FPG, was steeper for H- than for F-prediabetes. Thus, H-prediabetes was approximately four times more prevalent among participants aged ≥ 70 years of age

than among those aged 40–49 years, as against a factor of only three for F-prediabetes.

Logistic regression analysis showed that age, BMI, MCH, uric acid, LDL cholesterol, diastolic blood pressure and fasting insulin were all associated with HoF-prediabetes, whereas sex, current smoking, systolic blood pressure, HDL cholesterol, triglycerides, creatinine and the use of drugs that affect glucose metabolism were not (Table 2). After similar analyses had been performed for H-, F- and HaF-prediabetes, the risk factors common to all these varieties of prediabetes were age (the most influential), LDL cholesterol and fasting insulin. H-prediabetes was additionally associated with BMI and MCH, F-prediabetes with male sex and uric acid, and HaF-prediabetes with BMI. Men had significantly higher uric acid levels than women (365 ± 78 mmol/L vs 268 ± 73 mmol/L, $P < 0.001$). Strikingly, among the 148 participants with MCH < 28 pg (11.1% of all participants; 5.0% of men and 15.9% of women), the prevalence of H-prediabetes was 27.7%, as against only 17% among the 279 with MCH ≥ 31 pg (21%; 28.8% of men and 15.1% of women) ($P < 0.01$).

In the whole study group, HbA_{1c} and FPG both correlated significantly with age ($r = 0.480$ and $r = 0.378$, respectively; $P < 0.001$ in both cases) and similar associations held among the normoglycemic participants ($r = 0.423$ for HbA_{1c} and $r = 0.287$ for FPG, $P < 0.001$ in both cases). In both these groups, the age group means of FPG were practically unchanged when adjusted for sex, BMI, fasting insulin, LDL cholesterol, uric acid and MCH and the age group means of HbA_{1c} were similarly unaltered when adjusted for these factors plus FPG, or for FPG alone (Supplementary Table 3).

With a view to increasing the efficiency of screening for prediabetes, it is of interest to consider the effect of using known risk factors for pre-screening, i.e., of measuring FPG and/or HbA_{1c} preferentially in individuals with known risk factors for prediabetes. Table 3 shows the sensitivity of hypertension, hyperlipidemia, obesity and hyperuricemia, and of combinations of these risk factors, for detection of prediabetes. The most sensitive individual risk factor was obesity (sensitivity 0.529), while the sensitivities of hypertension, hyperlipidemia and hyperuricemia were very similar (0.426, 0.423 and 0.411, respectively). Including hyperuricemia as an alternative pre-screening criterion increased the sensitivity of all the others, the increase ranging from about 6% for the compound criterion "hypertension or hyperlipidemia or obesity" (increased from 0.768 to 0.831) to 25% for hyperlipidemia (increased from 0.423 to 0.673). The group of participants with hypertension or hyperlipidemia or obesity or hyperuricemia, who made up 59.9% of the whole study group, thus included 83.1% of all prediabetic participants. Including the additional alternative pre-screening criterion "age > 44 years" (satisfied by 74% of all the prediabetic participants) identified 1002 individuals (75.5% of the whole study group), a group that included 96% of all prediabetic participants.

Discussion

In this community-based study of Spanish subjects aged ≥ 18 years, the risk factors for H- and F-prediabetes differed more or less as previously reported [5, 8, 10, 13, 16, 27], but not after adjustment by other covariates. In multiple regression models, increasing age, LDL cholesterol and fasting insulin are risk factors common to both H- and F-prediabetes. Increasing BMI and diminishing MCH

Table 2 Odds ratios and their 95% CIs for risk factors associated with the various types of prediabetes[a] in multivariable analyses

Variables	OR (95% CI)			
	HoF-prediabetes	H-prediabetes	F-prediabetes	HaF-prediabetes
Age (per year)	1.06 (1.05–1.07)*	1.06 (1.05–1.07)*	1.05 (1.04–1.06)*	1.06 (1.05–1.08)*
Male sex	–	–	1.60 (1.06–2.41)‡	–
BMI (per kg/m^2)	1.05 (1.02–1.09)†	1.09 (1.05–1.13)*	–	1.07 (1.02–1.13)†
MCH (per pg)	0.91 (0.83–0.99)‡	0.82 (0.75–0.89)*	–	–
Uric acid (per 50 mmol/L)	1.15 (1.04–1.27)†	–	1.20 (1.07–1.35)†	–
LDL cholesterol (per mmol/L)	1.02 (1.00–1.04)‡	1.02 (1.00–1.04)‡	1.04 (1.01–1.06)†	1.04 (1.01–1.07)†
Fasting insulin (per mU/L)	1.08 (1.06–1.11)*	1.03 (1.01–1.06)†	1.10 (1.08–1.13)*	1.07 (1.04–1.09)*
Diastolic blood pressure (per mmHg)	1.02 (1.00–1.04)‡	–	–	–

Only statistically significant values are shown. Odds ratios (OR) are for prediabetes versus normoglycemia. ORs are adjusted for the other covariates appearing above, plus smoking, systolic blood pressure, HDL cholesterol, triglycerides, creatinine and use of GMA drugs (pharmaceutical drugs that can affect glucose metabolism)

[a]H, HbA_{1c} 5.7–6.4% (39–47 mmol/mol); F, FPG 5.6–6.9 mmol/L; HaF, HbA_{1c} 5.7–6.4% (39–47 mmol/mol) and FPG 5.6–6.9 mmol/L; HoF, HbA_{1c} 5.7–6.4% (39–47 mmol/mol) or FPG 5.6–6.9 mmol/L

*$P < 0.001$; †$P < 0.01$; ‡$P < 0.05$

Table 3 Prevalence of HoF-prediabetes in risk factor groups, and sensitivity of the risk factor for HoF-prediabetes

Risk factors	All *n*	HoF-prediabetic	Sensitivity[a]	*P**
None	521	62 (11.9)	15.6	
Hyperuricemia	387	163(42.1)	41.1	< 0.001
Hypertension	312	169 (54.2)	42.6	
Hypertension or hyperuricemia	564	248 (44.0)	62.5	< 0.001
Hyperlipidemia	347	168 (48.4)	42.3	
Hyperlipidemia or hyperuricemia	614	267 (43.5)	67.3	< 0.001
Obesity	416	210 (50.5)	52.9	
Obesity or hyperuricemia	611	266 (43.5)	67.0	< 0.001
Hypertension or hyperlipidemia	500	237 (47.4)	59.7	
Hypertension or hyperlipidemia or hyperuricemia	701	297 (42.4)	74.8	< 0.001
Hypertension or obesity	558	275 (49.3)	69.3	
Hypertension or obesity or hyperuricemia	708	307 (43.4)	77.3	0.011
Hyperlipidemia or obesity	601	282 (46.9)	71.0	
Hyperlipidemia or obesity or hyperuricemia	748	319 (42.6)	80.4	0.002
Hypertension or hyperlipidemia or obesity	672	305 (45.4)	76.8	
Hypertension or hyperlipidemia or obesity or hyperuricemia	796	330 (41.5)	83.1	0.027

Data are *n*, *n*(%), or %

[a]Sensitivity for detecting participants with HoF-prediabetes (397), as a percentage

*For comparison with groups without hyperuricemia

were additional risk factors for H-prediabetes, male sex and increasing uric acid concentration for F-prediabetes, and increasing BMI for HaF-prediabetes. The most influential risk factor in all cases was increasing age.

While H- and F-prediabetes are invariably reported to have different prevalences, some studies find the more prevalent to be F-prediabetes [7–12, 16, 23] and others, like the present study, H-prediabetes [13, 18, 24–28]. Since both H- and F-prediabetes include persons excluded by the other, the prevalence of HoF-prediabetes is greater than that of either. Many factors may contribute to these differences [4–6]: One is age. In the present study we observed, like others [29–32], an increase in HbA_{1c} with age, by about 0.1% per decade when unadjusted (a figure similar to that of a previous report [31]) and about 0.06% per decade when adjusted for FPG or for FPG, sex, BMI, fasting insulin, MCH, LDL cholesterol and uric acid. In the normoglycemic subgroup, the rate of increase was slightly smaller but quite clear. This increase in HbA_{1c} with increasing age, which is consistent with the notion that the glycation of hemoglobin is accelerated by aging [31], may partly explain the differences in the prevalence of H-prediabetes between studies of subjects aged ≥ 18 years [8–10, 12, 25, 26, 28] and studies that only included subjects with baseline ages > 40 years [7, 8, 13, 23, 24]. It may also partly explain why, in the present study, in which participants who were taking GMA drugs were on average 13 years older than those who were not, H-prediabetes was more than twice as prevalent among the GMA drug takers as among the others (30.1% vs 13.8%); after adjusting for age, there was no significant difference between the mean HbA_{1c} levels of these two groups (5.38% vs 5.42%, $P = 0.061$).

The prevalence of H-prediabetes was similar among men and women, but men were much more likely than women to have F-prediabetes, as previously reported [12, 23]. Although uric acid levels were higher in men than in women, male sex and uric acid were nevertheless mutually independent risk factors for F-prediabetes after adjusting for creatinine and other confounders. Although Japanese subjects with F-prediabetes have been reported to have elevated uric acid levels [16], as far as we know, this is the first time it has been shown that a relationship between uric acid and the prevalence of F-prediabetes persists after adjustment for other covariates and that no such relationship holds in the case of H-prediabetes.

Although the reasons for the above difference between H- and F-prediabetes are unknown, it is possible that the effects of sex and uric acid on nonglycemic determinants of HbA_{1c} differ from their effects on glycemic determinants. Among the nonglycemic influences on HbA_{1c} are those affecting erythrocyte turnover. We recently found that for at least 25% of all patients for whom an analytical profile is requested that includes the relevant determinations, low or high MCH levels are associated with increased risk of an erroneous HbA_{1c}-based identification of glycemia status [33]. In the present study, after adjustment for sex, age and other confounders, the odds ratio of H-prediabetes prevalence fell by 18% (95% CI 11–25%) for each pg increase in

MCH, and differences of about 3 pg were observed between the extremes of the MCH distributions. Accordingly, MCH may at least partially explain the discrepancies between the results of using HbA_{1c} and FPG criteria for diagnosis of prediabetes.

In these nondiabetic subjects, BMI was a risk factor for H-prediabetes but not for F-prediabetes, and in the HoF-prediabetic group, increasing BMI was accompanied by an increase in the proportion who were F-prediabetic, but a slight decrease in the proportion who were H-prediabetic (whereas others have reported the opposite behavior [34]). These differences are probably due to FPG and HbA_{1c} reflecting different domains of glucose metabolism (as noted above, in this study FPG correlated better with fasting insulin than with HbA_{1c}). F-prediabetes is mostly a dysfunction of hepatic insulin resistance, whereas HbA_{1c}, which represents chronic exposure over 2–3 months to both basal and postprandial hyperglycemia, may reflect a combination of both hepatic and muscular insulin resistance [5, 35].

This study was novel in comparing different criteria of prediabetes in regard to their associated risk factors and in regard to their estimated prevalence after adjustment for confounders. The reliability of its results is supported by its participants having come from a representative sample of an ethnically homogeneous (100% Caucasian) general population, by their constituting 70% of the accessible and eligible members of this sample, making significant bias unlikely, and by all analyses having been performed by the same method in the same laboratory on the day the blood sample was obtained. However, the limitations of this study should also be borne in mind. An obvious limitation was that OGTT results were not obtained, so we could not evaluate how well HbA_{1c} and FPG perform in comparison with 2-h plasma glucose. However, in many centers, the OGTT is not routinely performed in clinical practice; it is the comparison between FPG and HbA_{1c} that is clinically more important. A somewhat more subtle shortcoming was that FPG and HbA_{1c} were only determined once even though they can change over time, and small differences in HbA_{1c} can have a disproportionately large impact on glycemic status. However, sensitivity analysis suggests that our findings will not have been greatly affected in this way: lowering the HbA_{1c} threshold for H-prediabetes to 38 mmol/mol had an insignificant effect on our results [8]. Finally, although the ethnic homogeneity of our sample was an advantage from the point of view of the robustness of the results, it also means that these results may not be generalizable to other racial or ethnic groups.

In summary, in this community sample of nondiabetic adults, the most important risk factor for prediabetes and hence for diabetes and cardiovascular disease, was age, followed by fasting insulin and LDL cholesterol. Additional risk factors for IFG were male sex and uric acid concentration, and additional risk factors for HbA_{1c}-defined prediabetes were BMI and MCH, while BMI was also an additional risk factor for simultaneous satisfaction of both the FPG and HbA_{1c} criteria of prediabetes. The group of individuals with hypertension or obesity or dyslipidemia or hyperuricemia (who together made up 60% of the whole study group) included 83% of those with prediabetes by at least one criterion, suggesting that programs to prevent progress from prediabetes to diabetes might profitably screen individuals with these risk factors. Although the definition of HbA_{1c}-defined prediabetes would seem clear, it is called into question by the relationship between HbA_{1c} and MCH, an indirect measure of erythrocyte survival: The prevalence of HbA_{1c}-defined prediabetes was 17% among high-MCH individuals (21% of our subjects), but rose to 28% among individuals with low MCH (11% of our subjects). In view of our findings, further studies are needed to evaluate the risk of adverse long-term developments for persons with these different types of prediabetes.

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Authors contribution Dr. Santiago Rodriguez-Segade is the guarantor of this work and, as such, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. SRS designed, researched and wrote the manuscript. JR, LSP, JGJ, MPC JMGL, MAS, ALQ and FG research data and contributed to discussion. FC contributed to discussion, edited the manuscript and made artwork. The final version of the manuscript was approved by all authors.

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Compliance with ethical standards

Conflict of interest The authors declare that there is no duality of interest associated with this manuscript.

Ethical approval The study was reviewed and approved by the clinical research ethics committee of Galicia, Spain (CEIC 2012-025) and conformed with the current Helsinki Declaration.

Informed consent Written informed consent was obtained from each participant.

References

1. American Diabetes Association (2010) Diagnosis and classification of diabetes mellitus. Diabetes Care 33(Suppl. 1):S62–S69

2. Inzucchi SE (2012) Diagnosis of diabetes. N Engl J Med 367:542–550
3. American Diabetes Association (2017) Classification and diagnosis of diabetes mellitus. Secion 2. In Standards of Medical Care in Diabetes-2017. Diabetes Care 40(1):S11–S24
4. Diabetes Prevention Program Research Group (2002) Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 346:393–403
5. Goldstein DE, Little RR, Lorenz RA et al (2004) Tests of glycemia in diabetes. Diabetes Care 27:1761–1773
6. Sacks DB (2011) A1C versus glucose testing: a comparison. Diabetes Care 34:518–523
7. Warren B, Pankow JS, Matsushita K et al (2017) Comparative prognostic performance of definitions of prediabetes: a prospective cohort analysis of the Atherosclerosis Risk in Communities (ARIC) study. Lancet Diabetes Endocrinol 5(1):34–42
8. Mann DM, Carson AP, Shimbo D, Fonseca V, Fox CS, Muntner P (2010) Impact of A1C screening criterion on the diagnosis of pre-diabetes among U.S. adults. Diabetes Care 33:2190–2195
9. Olson DE, Rhee MK, Herrick K, Ziemer DC, Twombly JG, Phillips LS (2010) Screening for diabetes and pre-diabetes with proposed HbA1C-based diagnostic criteria. Diabetes Care 33:2184–2189
10. James C, Bullard KM, Rolka DB et al (2011) Implications of alternative definitions of prediabetes for prevalence in US adults. Diabetes Care 34:387–391
11. Nowicka P, Santoro N, Liu H et al (2011) Utility of hemoglobin HbA1C for diagnosing prediabetes and diabetes in obese children and adolescents. Diabetes Care 34:1306–1311
12. Pinelli NR, Jantz AS, Martin ET, Jaber LA (2011) Sensitivity and specificity of glycated haemoglobin as a diagnostic test for diabetes and prediabetes in Arabs. J Clin Endocrinol Metab 96:E1680–E1683
13. Saukkonen T, Cederberg H, Jokelainen J et al (2011) Limited overlap between intermediate hyperglycemia as defined by A1C 5.7–6.4%, impaired fasting glucose, and impaired glucose tolerance. Diabetes Care 34(10):2314–2316
14. Tankova T, Chakarova N, Dakovska L, Atanassova I (2012) Assessment of HbA_{1c} as a diagnostic tool in diabetes and prediabetes. Acta Diabetol 49:371–378
15. Sumner AE, Duong MT, Aldana PC et al (2016) A1C combined with glycated albumin improves detection of prediabetes in Africans: the Africans in America Study. Diabetes Care 39:271–277
16. Heianza Y, Hara S, Arase Y et al (2011) HbA_{1c} 5.7–6.4% and impaired fasting plasma glucose for diagnosis of prediabetes and risk of progression to diabetes in Japan (TOPICS 3): a longitudinal cohort study. Lancet 378:147–155
17. Lipska KJ, Inzucchi SE, Van Ness PH et al (2013) Elevated HbA_{1c} and fasting plasma glucose in predicting diabetes incidence among older adults. Are two better than one? Diabetes Care 36:3923–3929
18. Eastwood SV, Tillin T, Sattar N, Forouhi NG, Hughes AD, Chaturvedi N (2015) Associations between prediabetes, by three different diagnostic criteria, and incident CVD differ in south Asians and Europeans. Diabetes Care 38:2325–2332
19. Diabetes Prevention Program Research Group (2015) HbA1c as a predictor of diabetes and as an outcome in the diabetes prevention program: a randomized clinical trial. Diabetes Care 38:51–58
20. Anjana RM, Shanthi Rani CS, Deepa M et al (2015) Incidence of diabetes and prediabetes and predictors of progression among Asian Indians: 10-year follow-up of the Chennai Urban Rural Epidemiology Study (CURES). Diabetes Care 38:1441–1448
21. Gude F, Díaz-Vidal P, Rúa-Pérez C et al (2017) Glycaemic variability and its association with demographics and lifestyles in a general adult population. J Diabetes Sci Technol 11:780–790
22. Hoelzel W, Weykamp C, Jeppsson JO et al (2004) IFCC reference system for measurement of haemoglobin HbA 1C in human blood and the National Standardization Schemes in the United States, Japan, and Sweden: a method-comparison study. Clin Chem 50:166–174
23. Lipska KJ, De Reheneire N, Van Ness PT et al (2010) Identifying dysglycaemic states in older adults: implications of the emerging use of haemoglobin HbA1c. J Clin Endocrinol Metab 95:5289–5295
24. Mostafa SA, Davies MJ, Webb D et al (2010) The potential impact of using glycated haemoglobin as the preferred diagnostic tool for detecting type 2 diabetes mellitus. Diabet Med 27:762–769
25. Cosson E, Chiheb S, Cussac-Pillegand C et al (2013) Haemoglobin glycation may partly explain the discordance between HbA1c measurement and oral glucose tolerance test to diagnose dysglycaemia in overweight/obese subjects. Diabetes Metab 39:118–125
26. Li J, Ma H, Na L et al (2015) Increased Hemoglobin A1c threshold for prediabetes remarkably improving the agreement between A1c and oral glucose tolerance test criteria in obese population. J Clin Endocrinol Metab 100:1997–2005
27. Rosella LC, Lebenbaum M, Fitzpatrick T, Zuk A, Booth GL (2015) The prevalence of undiagnosed and prediabetes diabetes in Canada (2007–2011) according to fasting plasma glucose and HbA_{1c} screening criteria. Diabetes Care 38:1299–1305
28. Ho-Pham LT, Do TT, Campbell LV, Nguyen TV (2016) HbA_{1c}-based classification reveals epidemic of diabetes and prediabetes in Vietnam. Diabetes Care 39:e93–e94
29. Hashimoto Y, Futamura A, Ikushima M (1995) Effect of aging on HbA1c in a working male Japanese population. Diabetes Care 18:1337–1340
30. Nuttall QF (1999) Effect of age on percentage of hemoglobin A1c and the percentage of total glycohemoglobin in non-diabetic persons. J Lab Clin Med 134:451–453
31. Pani LN, Korenda L, Meigs JB et al (2008) Effect of aging on A1C levels in individuals without diabetes. Evidence from the Framingham offspring study and the National Health and Nutrition Examination Survey 2001–2004. Diabetes Care 31:1991–1996
32. Selvin E, Zhu H, Brancati FL (2009) Elevated A1C in adults without a history of diabetes in the U.S. Diabetes Care 32:828–833
33. Rodriguez-Segade S, Rodriguez Garcia J, Garcia-Lopez JM et al (2016) Impact of mean cell hemoglobin on HbA_{1c}-defined glycemia status. Clin Chem 62:1570–1578
34. Lorenzo C, Wagenknecht LE, Hanley AJG, Rewers MJ, Karter AJ, Haffner SM (2010) A1C between 5.7 and 6.4% as a marker for identifying pre-diabetes, insulin sensitivity and secretion, and cardiovascular risk factors. Diabetes Care 33:2104–2109
35. International Expert Committee (2009) International Expert Committee report on the role of the A1C assay in the diagnosis of diabetes. Diabetes Care 32:1327–1334